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ORAL ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALY AVAILABLE THERAPIES

Itacitinib for the Prevention of Immune Effector Cell Therapy-Associated Cytokine Release Syndrome: Results from the Phase 2 Incb 39110-211 Placebo-Controlled Randomized Cohort

Matthew J. Frigault, MD MS¹, Richard T Maziarz, MD², Jae H. Park, MD³, Aleksandr Lazaryan, MD MPH, PhD⁴, Nirav N. Shah, MD⁵, Jakub Svoboda⁶, Lazaros J. Lekakis⁷, Ran Reshef, MD⁸, Christine L Phillips, MD⁹, Lea M Burke, MS¹⁰, Jing Lei¹¹, Rodica Morariu-Zamfir¹⁰, John F. DiPersio, MD PhD¹²

¹Massachusetts General Hospital, Dorchester, MA

²Knight Cancer Institute, Oregon Health & Science University, Portland, OR

³Memorial Sloan Kettering Cancer Center, New York, NY

⁴Department of Blood and Marrow Transplantation and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL

⁵Medical College of Wisconsin, Milwaukee, WI

⁶University of Pennsylvania, Philadelphia, PA

⁷University of Miami, Miami, FL

⁸Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY

⁹Division of Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

¹⁰Incyte Corporation, Wilmington, DE

¹¹Incyte, Wilmington, DE

¹²Washington University School of Medicine, Saint Louis, MO

Introduction: Cytokine release syndrome (CRS) and immune effector cell (IEC)-associated neurotoxicity syndrome (ICANS) are common adverse effects following IEC therapy. Janus kinase (JAK) pathways are important for the signaling of several cytokines involved in CRS pathogenesis. Itacitinib is a potent, selective JAK1 inhibitor with broad anti-inflammatory activity. We describe preliminary results from the randomized, placebo-controlled portion of the study evaluating itacitinib 200 mg twice daily (bid) for the prevention of CRS.

Methods: This randomized, placebo-controlled portion of the phase 2 Study INCB 39110-211 (NCT04071366) enrolled patients ≥ 18 years old planning to receive axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma (rrLBCL) and follicular lymphoma (rrFL). Participants received oral itacitinib 200 mg bid beginning 3 days before axicabtagene ciloleucel infusion and continued itacitinib through Day 26. Protocol did not allow tocilizumab for treatment of grade 1 CRS unless CRS did not improve after 72 hours of supportive treatment. Patients who received tocilizumab for grade 1 CRS were not censored. Primary endpoint was incidence of CRS grade ≥ 2 by Day 14 using American Society for Transplantation and Cellular Therapy grading system. Secondary endpoints included incidence of ICANS by Day 28, duration of CRS and ICANS, and itacitinib safety.

Results: 47 patients with rrLBCL were randomized to itacitinib (n=23; median age, 66 [range: 29-80] years; male, 65%) or placebo arms (n=24; median age, 64 [range: 31-79] years; male, 71%). Median (range) number of prior regimens was 2 (1-6) and 1.5 (1-4), respectively. No rrFL patients enrolled in the study. Two (8%) patients in the itacitinib arm received platelet transfusions after Day 28; no transfusions were received in the placebo group.

A total of 15 (65.2%) patients in the itacitinib arm developed CRS (grade 1, n=11 [47.8%]) compared with 20 (87.0%) patients in placebo arm (grade 1, n=7 [30.4%]; Figure). No hypotension or hypoxia was observed in patients with grade 1 CRS who received tocilizumab. Grade 2 CRS was experienced by 4 (17.4%) and 13 (56.5%) patients, respectively (P=0.003; 95% CI: 0.14-0.65). There was no grade 3 or 4 CRS in either arm. Median (range) time to any-grade CRS onset was 2 (0-8) days and 3 (0-9) days, respectively; median (range) duration of grade 2 CRS was 2 (1-8) and 2 (1-5) days. Overall, tocilizumab was used for CRS treatment in 4 (17.4%) patients in the itacitinib arm and in 15 (65.2%) patients in the placebo arm, including 2 and 6 patients, respectively, who received tocilizumab for grade 1 CRS. ICANS occurred in 3 (13%; 95% CI: 3-34) patients in the itacitinib arm and 8 (34.8%; 95% CI: 16-57) patients in the placebo arm (Figure). ICANS grade ≥ 2 was reported in 2 (8.6%; 95% CI: 1-28) and 5 (21.7%; 95% CI: 8-44) patients, respectively. No grade 4 ICANS occurred in either arm. Median (range) time to

any-grade ICANS onset was 5 (4-9) days and 6.5 (2-11) days, respectively; median (range) duration was 2 (2-11) and 3.5 (2-13) days.

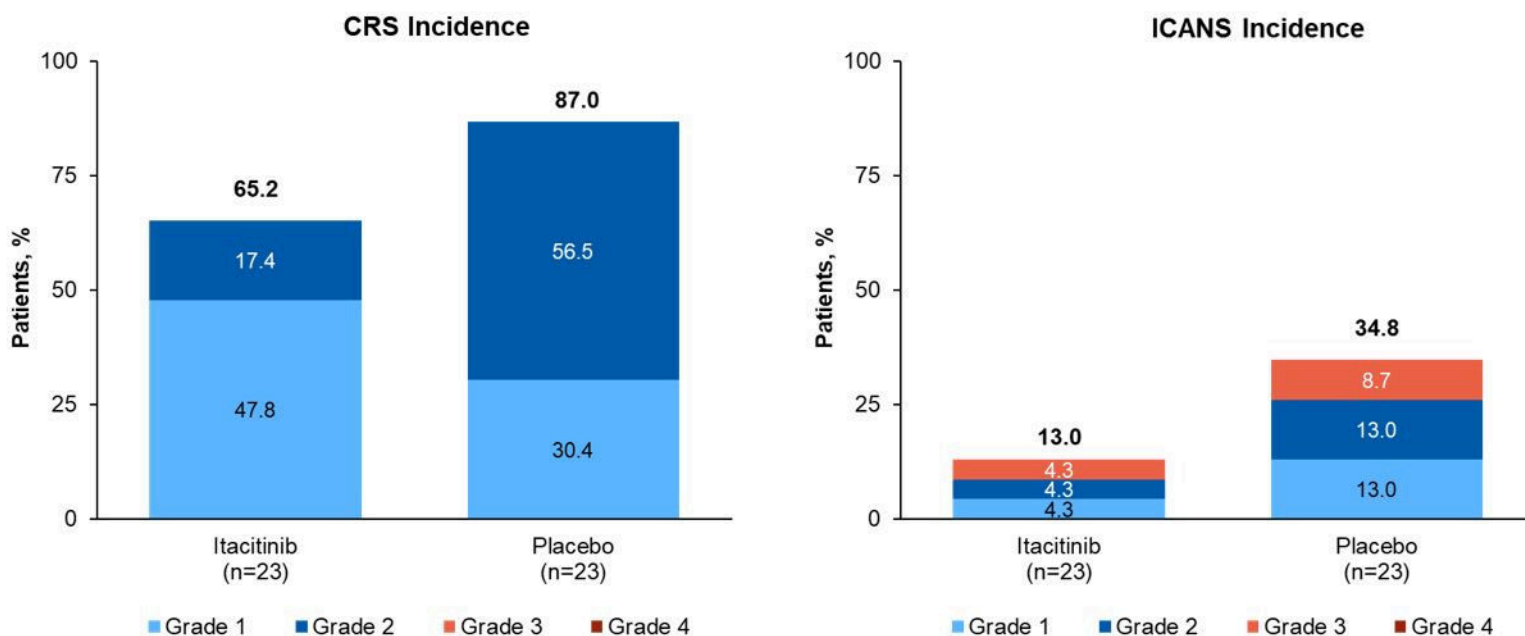
Persistent grade 3 or 4 thrombocytopenia at Day 28 in the itacitinib arm was reported in 8 (38.1%; [grade 4: n=4]) patients; in the placebo arm in 4 (18.2%; [grade 4: n=0]) patients. Persistent grade 3 or 4 neutropenia at Day 28 in the itacitinib arm was reported in 7 (33.3%; [grade 4: n=3]) patients; in the placebo arm in 3 (13.6%; [grade 4: n=0]) patients. Infections grade ≥ 3 occurred before Day 28 in 2 (8.7%) patients in the itacitinib arm (urinary tract infection [UTI], n=2) and in 3 (12.5%) patients in the placebo arm (sepsis, n=2; UTI, n=1). There were no fatal adverse events. With a minimum follow-up of 28 days, lymphoma best overall response to axicabtagene ciloleucel showed no difference between the 2 arms.

Conclusions: Results from the randomized, placebo-controlled portion of Study INCB 39110-211 have shown prophylaxis treatment with itacitinib 200 mg bid to be well tolerated and resulted in a lower rate and grade of CRS and ICANS after lymphoma treatment with axicabtagene ciloleucel. Incidence of grade 3/4 neutropenia and thrombocytopenia not resolved at Day 28 was higher with itacitinib vs placebo. Rates of severe infections were comparable in both arms. Longer follow-up data on lymphoma response will be available upon presentation. Biomarker analyses comparing the effect of itacitinib on CAR-T cells expansion and function are ongoing.

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Figure. CRS and ICANS Incidence by Grade in Itacitinib and Placebo Arms



CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

Figure 1